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(71) Applicant *(for GB only)*: PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant *(for all designated States except GB JP US)*: PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A. [BE/IE]; La Touche House, International Financial Services Centre, Dublin 1 (IE).

(71) Applicant *(for JP only)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CAMPBELL, Simon, Fraser [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MACKENZIE, Alexander, Roderick [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). WOOD, Anthony [GB/GB]; Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: MOORE, James, William et al.; Pfizer Limited, European Patent Dept., Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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(54) Title: cGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

(57) Abstract

Compounds which are selective inhibitors of cGMP PDE are useful in the treatment of erectile dysfunction (impotence) in male animals, including man.

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cGMP-PDE INHIBITORS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

This invention relates to the use of compounds which are selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) in the treatment of erectile dysfunction (impotence) in male animals, including man.

Impotence can be defined literally as a lack of power, in the male, to copulate and may involve an inability to achieve penile erection or ejaculation, or both. More specifically, erectile impotence or dysfunction may be defined as an inability to obtain or sustain an erection adequate for intercourse. Its prevalence is claimed to be between 2 and 7% of the human male population, increasing with age, up to 50 years, and between 18 and 75% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin.

Reports of well-controlled clinical trials in man are few and the efficacy of orally administered drugs is low. Although many different drugs have been shown to induce penile erection, they are only effective after direct injection into the penis, e.g. intraurethrally or intracavernosally (i.c.), and are not approved for erectile dysfunction. Current medical treatment is based on the i.c. injection of vasoactive substances and good results have been claimed with phenoxybenzamine, phentolamine, papaverine and prostaglandin E_1, either alone or in combination; however, pain, priapism and fibrosis of the penis are associated with the i.c. administration of some of these agents. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) have also been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side-effects in both patient and partner.

As a general alternative to pharmacological intervention, a variety of penile prostheses has been used to assist achievement of an erection. The short term

success rate is good, but problems with infection and ischaemia, especially in diabetic men, make this type of treatment a final option rather than first-line therapy.

According to the specification of our International patent application no PCT/EP94/01580, (publication no WO94/28902), we describe and claim the use of a series of pyrazolo [4,3-d]pyrimidin-7-ones for the treatment of impotence. The compounds are potent and selective inhibitors of cGMP PDE in contrast to their inhibition of cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP PDEs). This selective enzyme inhibition leads to elevated cGMP levels which, in turn, provides the basis for the utilities previously disclosed for the compounds in the treatment of stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, peripheral vascular disease, stroke, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, and diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome. The specification goes on to describe investigations which identified three PDE isoenzymes in human corpus cavenosum tissue, relaxation of which leads to penile erection. The predominant enzyme was found to be the cGMP-specific PDE_V, while cGMP-stimulated cAMP PDE_{II} and cGMP-inhibited cAMP PDE_{III}, were also present. The compounds described were found to be potent and selective inhibitors of the PDE_V enzyme but demonstrated only weak inhibitory activity against the PDE_{II} and PDE_{III} enzymes. This activity is believed to be responsible for the action of the compounds in the treatment of erectile dysfunction.

A number of cGMP-PDE inhibitors have previously been described in the literature for a variety of utilities, these include use in treating obstructive lung diseases such as asthma and brochitis, in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria, and irritable bowel syndrome; and in combatting angina, hypertension and congestive heart failure. Utility has also been claimed as diuretics, as antiinflammatory agents, in the treatment of baldness, for conditions of reduced blood vessel patency, and in glaucoma. However there has not previously been any suggestion that any of these compounds would be of utility in the treatment of erectile dysfunction.

Thus the present invention provides the use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

i a 5-substituted pyrazolo [4,3-d]pyrimidine-7-one as disclosed in European patent application 0201188;

ii a griseolic acid derivative as disclosed in European patent applications nos 0214708 and 0319050;

iii a 2-phenylpurinone derivative as disclosed in European patent application 0293063;

iv a phenylpyridone derivative as disclosed in European patent application 0347027;

v a fused pyrimidine derivative as disclosed in European patent application 0347146;

vi a condensed pyrimidine derivative as disclosed in European patent application 0349239;

vii a pyrimidopyrimidine derivative as disclosed in European patent application 0351058;

viii a purine compound as disclosed in European patent application 0352960;

ix a quinazolinone derivative as disclosed in European patent application 0371731;

x a phenylpyrimidone derivative as disclosed in European patent application 0395328;

xi an imidazoquinoxalinone derivative or its aza analogue as disclosed in European patent application 0400583;

xii a phenylpyrimidone derivative as disclosed in European patent application 0400799;

xiii a phenylpyridone derivative as disclosed in European patent application 0428268;

xiv a pyrimidopyrimidine derivative as disclosed in European patent 0442204;

xv a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

xvi a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in European patent application 0584487;

xvii a polycyclic guanine derivative as disclosed in International patent application WO91/19717;

xviii a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

xix a 2-benzyl-polycyclic guanine derivative as disclosed in International patent application WO 94/19351;

xx a quinazoline derivative as disclosed in US patent 4060615;

xxi a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US patent 5294612;

xxii a benzimidazole as disclosed in Japanese patent application 5-222000; or

xxiii a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.

xxiv a N-containing heterocycle as disclosed in International patent application WO94/22855.

The invention includes the use of any compound within the scope of the claims of the patents listed above as well as the particular individual compounds disclosed therein.

Of particular interest for use in the present invention are compounds disclosed in EP 0579496, WO93/07124, US 5294612 and WO94/22855 (xv, xviii, xxi and xxiv above); the compounds of EP 0579496 and WO94/22855 being especially preferred.

Examples of particular and preferred compounds from these patents and publications for use in the present invention include:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one (preparation as described in European patent application 201188, Example 1),

2-(2-propoxyphenyl)-6-purinone (preparation as described in European patent application 0293063, Example 1),

6-(2-propoxyphenyl)-l,2-dihydro-2-oxopyridine-3-carboxamide (preparation as described in European patent application 0347027, Example 2),

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one (preparation as described in European patent application 0347146, Example 1),
7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine (preparation as described in European patent application 0351058, Example 1),
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide (preparation as described in European patent application 0395328, Example 15),
1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one (preparation as described in European patent application 0400583),
4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline (preparation as described in European patent application 0579496, Example 5(c)),
5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine (preparation as described in European patent application 0584487, Example 1),
5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one (preparation as described in International patent application WO 91/19717, Example 9A3),
1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124),
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one(preparation as described in International Patent application WO94/19351, Example 14),
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90),
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one, (preparation as described in US patent 5294612, Example 83),
2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole (preparation described in Japanese patent application 5-222000),
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (preparation described in International patent application WO94/22855, Example II),
and 2-phenyl-8-ethoxycycloheptimidazole (KT2-734).

Of particular interest for use in the present invention are the compounds: 4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline (preparation as described in European patent application 0579496, Example 5(c)), 1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid (preparation as described in International patent application WO93/07124), (6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one(preparation as described in International Patent application WO94/19351, Example 14), 1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one (preparation as described in US patent 5294612, Example 90), 1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one, as described in US patent 5294612, Example 83), or 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline (preparation described in International patent application WO94/22855, Example II),

Further cGMP PDE inhibitors for use in the treatment of erectile dysfunction are:

xxv a pyrazolopyrimidine derivative as disclosed in European patent application 0636626;

xxvi a 4-aminopyrimidine derivative as disclosed in European patent application 0640599;

xxvii a imidazoquinazoline derivative as disclosed in International patent application WO95/06648;

xxviii an anthranilic acid derivative as disclosed in International patent application WO95/18097;

xxix a 4-aminoquinazoline derivative as disclosed in US patent 5436233;

xxx a tetracyclic derivative as disclosed in International patent application WO95/19978;

xxxi a imidazoquinazoline derivative as disclosed in European patent application 0668280; or

xxxii a quinazoline compound as disclosed in European patent application 0669324.

The compounds may be evaluated as selective inhibitors of cGMP-PDE using any of the methods previously described but in particular their activity against cGMP-PDE$_v$ may be assessed as described in our International patent application PCT/EP94/01580, (WO94/28902).

Generally, in man, oral administration is the preferred route, being the most convenient and avoiding the disadvantages associated with i.c. administration. A preferred dosing regimen for a typical man is 5 to 75 mg of compound daily, however the dosage may be increased depending on the potency of the compound being administered and higher dosages are within the scope of the invention. Alternative dosage regimes are also possible depending upon the individual patients circumstances such as the frequency of sexual intercourse. In circumstances where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, the drug may be administered parenterally, e.g. sublingually or buccally.

For veterinary use, a compound of the invention or a non-toxic salt thereof is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular male animal.

Although the compounds of the invention are envisaged primarily for the treatment of erectile dysfunction or male sexual dysfunction, they are also useful for the treatment of female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances, premature labour and dysmenorrhea.

The invention also provides a method of treating erectile dysfunction in a male animal which comprises administering an effective amount of a compound which is a selective cGMP-PDE inhibitor as defined above.

CLAIMS

1. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

i a 5-substituted pyrazolo [4,3-d]pyrimdine-7-one as disclosed in European patent application 0201188;

ii a griseolic acid derivative as disclosed in European patent applications nos 0214708 and 0319050;

iii a 2-phenylpurinone derivative as disclosed in European patent application 0293063;

iv a phenylpyridone derivative as disclosed in European patent application 0347027;

v a fused pyrimidine derivative as disclosed in European patent application 0347146;

vi a condensed pyrimidine derivative as disclosed in European patent application 0349239;

vii a pyrimidopyrimidine derivative as disclosed in European patent application 0351058;

viii a purine compound as disclosed in European patent application 0352960;

ix a quinazolinone derivative as disclosed in European patent application 0371731;

x a phenylpyrimidone derivative as disclosed in European patent application 0395328;

xi an imidazoquinoxalinone derivative or its aza analogue as disclosed in European patent application 0400583;

xii a phenylpyrimidone derivative as disclosed in European patent application 0400799;

xiii a phenylpyridone derivative as disclosed in European patent application 0428268;

xiv a pyrimidopyrimidine derivative as disclosed in European patent 0442204;

xv a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

xvi a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in European patent application 0584487;

xvii a polycyclic guanine derivative as disclosed in International patent application WO91/19717;

xviii a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

xix a 2-benzyl-polycyclic guanine derivative as disclosed in International patent application WO 94/19351;

xx a quinazoline derivative as disclosed in US patent 4060615

xxi a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US patent 5294612

xxii a benzimidazole as disclosed in Japanese patent application 5-222000; or

xxiii a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.

xxiv a N-containing heterocycle as disclosed in International patent application WO94/22855.

2. The use of a compound as claimed in claim 1 wherein said compound is:

a 4-aminoquinazoline derivative as disclosed in European patent application 0579496;

a nitrogenous heterocyclic compound as disclosed in International patent application WO93/07124;

a 6-heterocyclyl pyrazolo [3,4-d]pyrimid-4-one as disclosed in US patent 5294612 or

a N-containing heterocycle as disclosed in International patent application WO94/22855.

3. The use of a compound as claimed in claim 1 wherein said compound is:

1,3-dimethyl-5-benzylpyrazolo[4,3-d]pyrimidine-7-one;

2-(2-propoxyphenyl)-6-purinone;

6-(2-propoxyphenyl)-l,2-dihydro-2-oxopyridine-3-carboxamide;

2-(2-propoxyphenyl)pyrido[2,3-d]pyrimid-4(3H)-one;
7-methylthio-4-oxo-2-(2-propoxyphenyl)-3,4-dihydropyrimido[4,5-d]pyrimidine;
6-hydroxy-2-(2-propoxyphenyl)pyrimidine-4-carboxamide;
1-ethyl-3-methylimidazo[1,5a]quinoxalin-4(5H)-one;
4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;
5-ethyl-8-[3-(N-cyclohexyl-N-methylcarbamoyl)-propyloxy]-4,5-dihydro-4-oxo-pyrido[3,2-e]pyrrolo[1,2-a]pyrazine;
5'-methyl-3'-(phenylmethyl)-spiro[cyclopentane-1,7'(8'H)-(3'H)-imidazo[2,1-b]purin]4'(5'H)-one
1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;
2-butyl-1-(2-chlorobenzyl)6-ethoxycarbonylbenzimidazole;
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;
or 2-phenyl-8-ethoxycycloheptimidazole.

4. The use of a compound as claimed in claim 3 where said compound is:
4-phenylmethylamino-6-chloro-2-(1-imidazoloyl)quinazoline;
1-[6-chloro-4-(3,4-methylenedioxybenzyl)aminoquinazolin-2-yl)piperidine-4-carboxylic acid;
(6aR,9aS)-2-(4-trifluoromethylphenyl)methyl-5-methyl-3,4,5,6a,7,8,9,9a-octahydrocyclopent[4,5]imidazo[2,1-b]purin-4-one;
1-tert-butyl-3-phenylmethyl-6-(4-pyridyl)pyrazolo[3,4-d]pyrimid-4-one;
1-cyclopentyl-3-methyl-6-(4-pyridyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimid-4-one;
or
2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-nitroquinazoline;

5. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction in a male animal, including man, wherein said compound is:

xxv a pyrazolopyrimidine derivative as disclosed in European patent application 0636626;

xxvi a 4-aminopyrimidine derivative as disclosed in European patent application 0640599;

xxvii a imidazoquinazoline derivative as disclosed in International patent application WO95/06648;

xxviii an anthranilic acid derivative as disclosed in International patent application WO95/18097;

xxix a 4-aminoquinazoline derivative as disclosed in US patent 5436233;

xxx a tetracyclic derivative as disclosed in International patent application WO95/19978;

xxxi a imidazoquinazoline derivative as disclosed in European patent application 0668280; or

xxxii a quinazoline compound as disclosed in European patent application 0669324.

6. The use of a compound which is a selective cGMP PDE inhibitor for the manufacture of a medicament for the curative or prophylactic treatment of female sexual dysfunction, premature labour or dysmenorrhea, wherein said compound is a compound as previously claimed in any one of claims 1 to 5 for use in the treatment of erectile dysfunction in a male.

7. A method for the treatment of erectile dysfunction in a male animal or female sexual dysfunction, premature labour or dysmenorrhea, which comprises administering an effective amount of a compound which is a selective cGMP PDE inhibitor as previously claimed in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/EP 95/04066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AM.J.PHYSIOL., vol. 264, no. 2, 1993, pages 419-22, XP002000726 "Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs" see abstract see page 420, right-hand column, line 20 - line 24 see page 422, left-hand column, last paragraph ---	1-7
Y	EP,A,0 442 204 (SMITHKLINE BEECHAM) 21 August 1991 cited in the application see page 3, paragraph 1 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 1996	09 May 1996

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 293 063 (SMITH KLINE & FRENCH LAB.) 30 November 1988 cited in the application see page 2, paragraph 1 ---	1-7
Y	EP,A,0 371 731 (SMITHKLINE BEECHAM) 6 June 1990 cited in the application see page 2, paragraph 1 ---	1-7
Y,P	WO,A,94 29277 (SMITHKLINE BEECHAM) 22 December 1994 see page 1, paragraph 1 ---	1-7
Y,P	ABSTRACTS OF PAPERS AMERICAN CHEMICAL SOCIETY, vol. 210, no. 1-2, 1995, page MEDI 229. XP002000727 "uk-92480 a potent and selective inhibitor of type va cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction" abstract no. 229 -----	1-7

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/04066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 7 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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